

REMARKS

Claims 120-193 are pending in the present application. Entry of the amendments submitted herewith is respectfully requested, by which claims 120, 135, 153, 169, 186-188, 192 and 193 are amended to particularly point out and distinctly claim subject matter encompassed by certain embodiments of the present invention. The present amendments are made solely for purposes of advancing the prosecution of the application, without acquiescence in any rejection and without prejudice to the prosecution of any surrendered subject matter in this or any related continuation, continuation-in-part or divisional application. Amendment of claims 132 and 143 is also respectfully requested to correct an informality to which the PTO objected, namely a typographical error by which these claims recited “I_n” instead of “(C)_n”. Support for this amendment can be found in the specification at, *e.g.*, page 6, line 9; page 8, line 9; page 10, line 21; page 15, line 10; page 17, line 9; page 20, line 3; page 32, lines 16-21; and elsewhere.

Specifically, amendment of claims 120, 135, 153, 169, 186-188, 192 and 193 is respectfully requested so that these claims expressly recite “wherein the (antioxidant) compound exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity”, support for which can be found in the specification, for example, at page 81, lines 16-17 and Table 6, to distinguish the presently claimed chemically stable antioxidant compound over the prior art bromide salt of U.S. Pat. No. 6,331,532 (Murphy et al.) and its related continuation, U.S. Pat. No. 7,232,809. Decomposition data for the bromide salt of Murphy et al. are shown in the present application, for instance, in Table 2 at page 77, line 28 through page 78, line 3. No new matter is introduced by way of the present amendments.

It is submitted that the present amendment could not have been earlier made where applicants believe that, for reasons previously made of record, including those given in the response submitted on December 22, 2008, the instant embodiments are clearly patentable in view of the express feature “pharmaceutically acceptable anion” that is selected from “an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate”, as recited by the currently pending claims.

Indeed, according to the present Final Office Action, the PTO has withdrawn the previously asserted rejections under 35 U.S.C. §102 in view of applicants' December 22, 2008 amendment of the claims to recite this feature. In the present Final Action, however, the PTO now asserts new rejections under §103, to which the applicants have not previously been given an opportunity to respond. Applicants therefore submit that this new ground of rejection constitutes good and sufficient reason as to why the present amendment could not earlier have been presented.

Moreover, applicants traverse the assertion made by the PTO that applicants' amendment *necessitated* the new grounds of rejection presented in the current Office Action. On the contrary, the recited feature of the pharmaceutically acceptable anion that "does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety" can be found in the claims as *originally* filed and so would presumably have been the subject of the Examiner's earlier search and examination. Furthermore, it is submitted that the Examiner's allegation that this feature "does not constitute a patentable distinction **absent** a showing of criticality" (Action at page 3, lines 1-2 and 16-17, emphasis in original) should be reconsidered in view of the fact that the instant specification is rife with disclosure teaching this novel and nonobvious feature (*e.g.*, page 3, lines 17-19; page 4, line 13 through page 5, line 2; page 35, lines 3-18; page 36, lines 3-11). Hence, prior to the present Final Action applicants were unaware that the previously presented amendments, by which the "pharmaceutically acceptable anion" is specifically defined in the claims, would not, according to the PTO, suffice to place the claims in allowable condition, especially where the present rejections under §103 had not earlier been raised by the PTO.

It is therefore respectfully submitted that a showing has been made as to why the present amendment was not earlier presented. See M.P.E.P. §714.12. Entry of the amendment submitted herewith, and reconsideration of the application, are therefore respectfully requested.

APPLICATION INFORMALITIES

The Examiner objects to claims 132 and 143, alleging that "C of I_n" is unclear and requesting clarification.

Applicants thank the Examiner for pointing out these informalities and respectfully request correction of claims 132 and 143 by entry of the amendments to these claims as submitted herewith, to recite “(C)_n” instead of “I_n”. Support for these amendments can be found in the specification at, *e.g.*, page 6, line 9; page 8, line 9; page 10, line 21; page 15, line 10; page 17, line 9; page 20, line 3; and page 32, lines 16-21; and in, *e.g.*, original claims 8, 18, and 39. From these and other disclosures in the original application, it is submitted that it is readily apparent that the reference in the instant claims is to the feature “(C)_n” in the chemical structure of formula I as presented in base claims 130 and 141. Entry of the amendments, and reconsideration and withdrawal of the objections, are therefore respectfully requested.

REJECTIONS FOR NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

A. The PTO maintains the rejections of claims 120-185, 192 and 193 for alleged non-statutory obviousness-type double patenting over claims 1-10 of U.S. Patent 7,232,809 (Murphy et al.). In particular, the Examiner alleges that the “criticality” of the recited anions to the improved properties of the antioxidant compounds has not been shown.

Applicants respectfully traverse these grounds for rejection. The instant embodiments are directed in pertinent part to a chemically stable antioxidant compound comprising a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and an anionic complement for said cationic moiety, wherein the cationic moiety is capable of mitochondrially targeting the antioxidant moiety, wherein the anionic complement is a pharmaceutically acceptable anion that is not a halogen ion or a nitrate anion and is selected from an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate, and does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety, and wherein the antioxidant compound exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity.

For reasons given herein and previously made of record, including in the application as originally filed and in applicants’ response of December 22, 2008, the presently claimed subject matter relates to patentably distinct species. Only in the present application is

the problem of instability of the subject lipophilic cation-linked antioxidants disclosed for the first time, including the unexpected finding that bromide salts of the antioxidant compounds made according to U.S. Patent 7,232,809 (which is a continuation of U.S. 6,331,532) are disadvantageously unstable (*e.g.*, present specification at page 3, line 8 through page 5, line 9; Example 7 at pages 73-79). Further, only in the present application is it disclosed for the first time that this problem can surprisingly be overcome, by the use of a non-halogen, non-nitrate, non-reactive pharmaceutically acceptable anion, as taught by the specification (*e.g.*, at page 35, lines 3-18; page 36, lines 3-11; page 3, lines 17-19; page 4, line 13 through page 5, line 2; Examples 8-10 at pages 79-87) and recited by the instant claims.

The present application also discloses unpredicted and unforeseen advantages of the presently claimed antioxidant compounds over those claimed in U.S. 7,232,809, by presenting stability data showing that the present compounds unexpectedly exhibited less than 10% decomposition after 60 days at 25°C, 50% relative humidity (*e.g.*, instant specification at page 81, lines 16-23 and Table 6), *i.e.*, under comparable conditions they were stable for over four times as long as compounds encompassed by the claims of U.S. 7,232,809 (*e.g.*, instant specification at page 77, Table 2).

As applicants have also previously pointed out (Response of December 22, 2008), the present application presents *in vivo* data showing that, unlike the instability exhibited by bromide salts of the prior art (discussed at, *e.g.*, page 3, line 8 through page 5, line 9), the instant compounds exhibited significant pharmacokinetic stability with appreciable concentrations persisting in the circulation 24 hours after intravenous or oral administration (*e.g.*, Example 11 at pages 86-91; see also Figure 31 and Table 12). The previously unforeseen advantages of the presently claimed subject matter for pharmaceutical uses are thus clearly disclosed in the instant application and could not have been predicted by the person having ordinary skill in the art, absent the teachings of the present application. The Examiner therefore errs in asserting that no patentable distinction has been demonstrated.

In the present case, the appropriate test for non-statutory obviousness-type double patenting is whether the invention defined in the instant claims would have been an obvious variation of the invention defined in one or more of claims 1-10 of U.S. 7,232,809. See M.P.E.P.

§804(II)[B](1)(a). In order to establish *prima facie* obviousness, the PTO must identify a reason why a chemist would have been led to modify a compound of U.S. 7,232,809 in the particular manner that would result in the subject matter encompassed by the instant claims, *e.g.*, that comprises one of the expressly recited anionic complements *and* that exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity. See *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 90 USPQ2d 1947, 1951 (Fed. Cir. 2009), citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.* 492 F3d 1350, 1356-57, 83 USPQ2d 1169 (Fed. Cir. 2007). The PTO fails to meet this burden.

In the current Office Action and also in the earlier Action of August 5, 2008, the PTO fails to articulate any such reasoning as to why the skilled person would have been led by the prior art to the presently claimed subject matter, nor has the Examiner even been able to point to any identification in the prior art of the problem of poor compound stability for the instant class of compounds, which problem is overcome by the presently claimed subject matter. Even assuming, *arguendo*, that the PTO were to rely on the assertion in the August 5, 2008, Action (at page 9) that the person having ordinary skill in the art were “to form the purpose of achieving acceptable an (*sic*) antioxidant compound”, applicants hasten to point out that this mere allegation lacks evidentiary basis as to why U.S. 7,232,809 would lead such a skilled artisan to use, from amongst myriad possible species that might be available for use as the anionic complement, the presently recited species of an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate.

Moreover, the PTO fails to provide evidence or reasoning as to why the skilled person would, with the requisite reasonable expectation of success, have been able to select an anion that *predictably* would provide an antioxidant compound that “exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity.” Applicants therefore respectfully submit that the presently recited subject matter could not reasonably have been predicted by the claims of U.S. 7,232,809, nor by any specification support for the claims in U.S. 7,232,809 (see M.P.E.P. §804(II)[B](1)).

According to the Court of Appeals for the Federal Circuit, unexpectedly improved properties can further rebut an allegation of obviousness. *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 90 USPQ2d at 1952. It is submitted that the presently encompassed subject matter is directed to antioxidant compounds having such unexpectedly improved properties that could not reasonably have been predicted from the cited patent, and therefore that the instant claims are patentably nonobvious over the claims of U.S. 7,232,809. Reconsideration and withdrawal of the rejection for nonstatutory obviousness-type double patenting are therefore respectfully requested.

B. Claims 120-185 and 192 stand rejected for non-statutory obviousness-type double patenting over claims 120, 122-128 and 130-133 of co-pending application number 11/355,518 and over claims 88-112 of co-pending application number 10/568,654 .

Applicants traverse these grounds of rejection and submit that the subject matter encompassed by the instant claims is patentably distinct over the cited co-pending applications, including for reasons given above and previously made of record.

As a first matter, applicants are confused by the assertion in the current Office Action that applicants' argument and amendments filed 22 December 2008 have been "fully considered". In particular, clarification is respectfully requested where it would appear that only a *provisional* double patenting rejection is appropriate here. It is not at all clear that applicants' previous efforts to point out the appropriateness of a *provisional* double patenting rejection have been "fully considered" insofar as in the current Office Action, the PTO is silent with respect to whether the present rejection is a *provisional* rejection.

On this point, it is submitted that the two applications cited in the present obviousness-type double patenting rejections are co-pending applications. Accordingly, and as applicants explicitly stated in the response of December 22, 2008, because the cited applications are co-pending, at most the PTO can assert a provisional double patenting rejection, which may be maintained in each application:

as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in at least one of the applications. M.P.E.P. § 804(I)(B).

It is therefore submitted that appropriate action can be taken by applicants at such time as the provisional double patenting rejection is the *only* remaining issue. The Examiner is urged to confirm that the present nonstatutory obviousness-type double patenting (ODP) rejections over claims 120, 122-128 and 130-133 of co-pending application number 11/355,518 and over claims 88-112 of co-pending application number 10/568,654 are provisional ODP rejections, or to otherwise explain why they are not.

Moreover, the subject matter of the instant claims is patentably distinct over the claims of the cited co-pending applications for reasons also given above, including the failure by the PTO to provide evidence or reasoning as to why, in the absence of the teachings of the present application, a person having ordinary skill in the art would have been led to an obvious variation of the subject matter of the cited co-pending claims. More specifically, the PTO fails to explain how, from the cited claims of the co-pending applications, the skilled person would have predicted the instant antioxidant compound that exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity and that comprises an anionic complement as recited, with the requisite reasonable expectation of success. As such, applicants submit the present claims are not in conflict with the cited claims of the cited co-pending applications, and no case of ODP is present.

Accordingly and in view of the foregoing, it is therefore submitted that the subject matter of the instant claims is patentably distinct over that of the cited co-pending applications. Reconsideration and withdrawal of the rejections are therefore respectfully requested.

C. The PTO rejects claim 134 under 35 U.S.C. §101 for alleged double patenting over claim 134 of co-pending application number 11/355,518 .

The rejection is traversed. As a first matter, in view of the amendments entered on December 22, 2008, and further upon entry of the amendments submitted herewith, and particularly in view of the dependency of instant claim 134 on base claim 120, it is submitted that instant claim 134 does not read on claim 134 of the cited co-pending application. As also discussed above, it is respectfully submitted that contrary to the assertion found in the Action, applicants' response of December 22, 2008, has not been "fully considered" where the Action is

silent on the question of whether this rejection should properly be a *provisional* rejection because the cited claim is currently pending in a co-pending application.

Applicants believe that because Application No. 11/355,518 remains co-pending to the best of applicants' knowledge at this time, a provisional double patent rejection is appropriate. According to M.P.E.P. § 804(II)(A), if the conflicting claims are in another co-pending application, form paragraph 8.31 ("*Rejection, 35 U.S.C. 101, Double Patenting*") should not be used, and instead a provisional double patenting rejection should be made using form paragraph 8.32.

Believing that at most a provisional double patenting rejection may be appropriate here, given applicants' belief that Application No. 11/355,518 remains co-pending, it is applicants' understanding that such a provisional double patenting rejection may be maintained in each application "as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in at least one of the applications". M.P.E.P. § 804(I)(B). At such time as this provisional double patenting rejection is the *only* rejection remaining in the present application, appropriate action will be taken. Clarification is respectfully requested if the Examiner believes a provisional double patenting rejection is not appropriate with respect to instant claim 134 in view of claim 134 of co-pending Application No. 11/355,518.

REJECTIONS UNDER 35 U.S.C. § 103

The PTO rejects claims 120-193 under 35 U.S.C. §103 for alleged obviousness over Murphy et al. (U.S. 6,331,532, "the '532 patent"). Specifically, the PTO alleges that the '532 patent broadly discloses an antioxidant moiety coupled to a lipophilic cation, in complex with an anion that is described *generically*, and concedes that the instant claims are directed more narrowly to such complexes having *specific* anionic species as expressly recited. The Examiner asserts that the '532 patent would have motivated the skilled person to make and use the claimed subject matter with a reasonable expectation of success "by evaluating different compounds employed as an (*sic*) that are commercially available to produce a chemically stable antioxidant compound of choice" (Action at page 6).

Applicants respectfully traverse these grounds for rejection. Contrary to the allegations found in the Action, the '532 patent fails to teach *or suggest* the features of the instant embodiments, which are directed in pertinent part to a chemically stable antioxidant compound comprising a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety; and an anionic complement for said cationic moiety, wherein the cationic moiety is capable of mitochondrially targeting the antioxidant moiety, wherein the anionic complement is a pharmaceutically acceptable anion that is not a halogen ion or a nitrate anion and is selected from an alkyl sulfonate, an aryl sulfonate, tetrafluoroborate, trifluoromethanesulfonate, hexafluoroantimonate, hexafluoroarsenate, hexafluorophosphate, tetraphenylborate, and tetra(perfluorophenyl)borate, and does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety, and wherein the antioxidant compound exhibits less than 10% decomposition after 60 days at 25°C, 50% relative humidity.

In addition to reasons discussed above and previously made of record in support of the nonobviousness of the claimed subject matter, it is submitted that problems associated with instability of antioxidant compounds prepared according to the teachings of the '532 patent were not recognized prior to the instant application, nor has the PTO presented any evidence to the contrary. Furthermore, the PTO also fails to present evidence that there was any suggestion in the prior art attributing such instability to the choice of anionic complement. Further still, the PTO fails to point to any prior art teaching that could have suggested which of the many possible anions should be used to obtain a stable product. As such, the PTO impermissibly employs hindsight in its allegation under "rational (*sic*) and motivation" (Action, bottom of page 5 through first two paragraphs of page 6) that the skilled person would have been motivated by the '532 patent to arrive at the presently claimed chemically stable antioxidant compound. The PTO further fails to establish that the '532 patent would have suggested the presently claimed subject matter to the skilled person with the *requisite* reasonable expectation of success.

It is axiomatic that obviousness is determined with respect to the claimed subject matter as a whole, and not to separate parts of the claim. *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). A proper analysis of the instant claims therefore should not be limited to consideration of the presently recited anions in isolation (Action, page 5, last paragraph), but

should instead be an analysis of the full scope of subject matter encompassed by the claim as a whole. Furthermore, the use of hindsight is inappropriate where teachings of the claimed invention are improperly read into the prior art. *KSR*, at 1742.

Here, the PTO points to no evidence whatsoever that the problem of poor stability had even been recognized for antioxidant compounds made according the '532 patent, nor does the PTO point to any suggestion in the prior art regarding how predictably to improve the stability of such compounds. Hence, the PTO fails to support its allegation that the "instantly claimed chemically stable antioxidant compound . . . would have been suggested to one of ordinary skill in view of the teachings of the prior art reference cited." (Action, page 6, lines 1-3). For reasons given herein, the prior art nowhere suggests to the person having ordinary skill that, in the context of the instant claim as a whole, any of the presently recited pharmaceutically acceptable anions could reasonably be expected to confer the recited properties (*e.g.*, "does not exhibit reactivity . . .", "exhibits less than 10% decomposition. . .") on the encompassed antioxidant compounds.

Applicants therefore respectfully submit that the PTO fails to establish *prima facie* obviousness where it fails to meet its burden of showing that all of the claimed elements were known in the prior art, that a person skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and that the combination would have yielded nothing more than predictable results to such a skilled person. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385. Additionally, the PTO fails to meet its burden of showing that the person skilled in the art would have had a reasonable expectation of success in arriving at the claimed subject matter. M.P.E.P. § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)).

Accordingly and as discussed above, it is submitted that the PTO fails to provide evidence or reasoning as to why the skilled person would reasonably have expected *successfully* to combine the recited elements. By alleging otherwise, the PTO impermissibly employs hindsight in view of the present application. "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the

prior art.” *KSR International Co. v. Teleflex Inc.*, 550 U.S. __, __, 127 S.Ct. 1727, 82 USPQ2d 1385, 1395 (2007), No. 04-1350 4, 14, (U.S. April 30, 2007).

In view of the foregoing, reconsideration of the application and an indication of the allowability of the claims are therefore respectfully requested. Should the Examiner believe that any issues remain outstanding in the present application, it is urged that a telephone inquiry please be made to the applicants’ undersigned representative at the Examiner’s earliest possible convenience.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable.
Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,
SEED Intellectual Property Law Group PLLC

/Stephen J. Rosenman/
Stephen J. Rosenman, Ph.D.
Registration No. 43,058

:
701 Fifth Avenue, Suite 5400
Seattle, Washington 98104
Phone: (206) 622-4900
Fax: (206) 682-6031

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